Research Article **ISSN: 2347-4882**

WORLD JOURNAL OF PHARMACOLOGICAL RESEARCH AND TECHNOLOGY

PHYTOCHEMICAL ESTIMATION AND ANTIPARKINSON POTENTIAL OF ARTICUM LAPPA

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ABSTRACT

Parkinson's disease (PD) is a complex, age-related neurodegenerative disease that causes neuronal loss and dysfunction over time. An imbalance of redox potential of oxidative stress in the cell causes neurodegenerative diseases and dysfunction of neurons. Plants are a rich source of bioactive substances that attenuate oxidative stress in a variety of neurological disorders. The study explored the anti-Parkinson potential of ethanolic extract from the roots of Articum lappa, attributing its efficacy to the high phenolic and flavonoid contents. Initial investigations involved the characterization of the plant's physiochemical and phytochemical profile, revealing a diverse array of bioactive compounds. The findings suggest that the aqueous extract of *Articum lappa* exhibits significant antioxidant properties and promising effects in animal models of Parkinson's disease. This research highlights the need for further clinical studies and activity-guided fractionations to enhance our understanding and application of *Articum lappa* in the development of new herbal drugs. By advancing these research directions, the therapeutic potential of *Articum lappa* extracts could be fully realized, potentially leading to innovative treatments for Parkinson's disease and other neurodegenerative disorders.

Keywords Parkinson's disease, *Arctium lappa*, Rotenone, Neurodegeneration, etc.

Received 1 May 2024, Revised 27 May 2024, Accepted 2 June 2024

INTRODUCTION

Neurological diseases encompass a wide range of disorders affecting the sensory system, including the brain, peripheral nerves, and spinal cord [1]. Neurodegenerative disorders, such as dementia, Parkinson's disease (PD), and motor neuron dysfunction, are marked by continuous neuronal damage and destruction due to factors like proteostasis disruption, neuroinflammation, oxidative stress, strain, and apoptosis. In Pakistan, approximately 450,000 individuals are afflicted with Parkinson's disease. The World Health Organization (WHO) reports that the mortality rate related to PD in Pakistan stands at 1.87% of the overall population [2,3].

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the progressive degeneration of dopaminergic neurons that extend from the substantia nigra (pars compacta) to the corpus striatum. First described by Dr. James Parkinson in his 1817 publication, "Essay on the Shaking Palsy," PD manifests in two forms: familial (genetically inherited) and sporadic (idiopathic) [4]. It is a slowly progressing disease that presents with both motor and nonmotor symptoms. Key signs and symptoms of PD include resting tremor, postural or gait abnormalities, muscle rigidity, and bradykinesia. A hallmark pathological feature of PD is the presence of Lewy bodies, which are clusters of α-synuclein-immunoreactive proteins, such as ubiquitin, that contribute to proteolysis and a decrease in dopaminergic neurons in the striatum, leading to reduced voluntary movements. As the disease advances, Lewy bodies spread to the neocortical and cortical regions [5,6]

Parkinson's disease (PD) typically manifests between the ages of 65 and 70 and is more prevalent in men than in women [7]. The neuropathological mechanisms underlying PD are multifactorial, involving a combination of genetic, nongenetic, and environmental factors. Key pathological mechanisms include the accumulation of protein aggregates, mitochondrial dysfunction, impaired protein clearance pathways, neuroinflammation, oxidative stress, excitotoxicity, and genetic mutations. Genetic factors account for only 5-10% of PD cases, with certain variant genes disrupting molecular pathways that lead to neurological dysfunction. Extensive genome-wide association studies (GWAS) have identified specific protein-encoding genes associated with these pathways, contributing to sporadic PD. Notable examples of these pathways include abnormalities in mitochondrial function and neuronal inflammation [8,9].

Current treatments for Parkinson's disease (PD) focus on alleviating symptoms without slowing disease progression or preventing dopaminergic neuron degradation. Various

guidelines recommend different treatments based on patient age and symptoms. Dopamine agonists are often used for younger patients, while levodopa is preferred for older patients. For initial therapy, MAO-B inhibitors are effective for patients experiencing early motor fluctuations, and COMT inhibitors can enhance the effects of levodopa when wearing-off symptoms occur. Pharmacological dopamine replacement and deep brain stimulation have proven highly effective in managing PD. Recent advances have improved patients' quality of life, and future strategies aim to identify individuals at high risk for developing PD. New formulations are being developed to enhance drug efficacy and reduce toxicity, and novel compounds such as β-asarone have shown promise against PD [10-12].

Several plant species have demonstrated significant therapeutic potential against neurodegenerative disorders, offering a range of protective effects that help mitigate neurodegeneration. Specifically, plants with antioxidant properties are widely recognized for their ability to ameliorate the disease process. These antioxidant-rich plants contribute to reducing oxidative stress, a key factor in neurodegenerative diseases, thereby providing a beneficial impact on disease progression and symptom management [13].

Arctium lappa, commonly referred to as greater ‘burdock’, gobo, edible burdock, or beggar’s button, is a Eurasian plant species belonging to the Asteraceae family. Initially cultivated in Asia and Europe, it has now spread to various climates and countries. This versatile plant has served various medicinal and culinary purposes, showcasing its enduring cultural and practical importance. The utilization of *Arctium lappa* as a nutritive food source and its extensive historical use in traditional medicine highlight its multifaceted role in different societies across the globe [14]. *A. lappa* has shown diverse pharmacological effects owing to the presence of diverse volatile and nonvolatile secondary metabolites like fatty acids, terpenes, flavonoids, lignans, acetylenic compounds, hydrocarbons, polysaccharides, phytosterols, terpenoids, aldehydes, carboxylic acids, fatty acids, monoterpenes, and sesquiterpenes [15,16]. So far, over 200 nonvolatile compounds have been isolated and identified from this genus. Earlier literature reported that this plants traditionally used in neurological disorders [17-19]. The present study was designed to assess the phytochemical estimation and antiparkinson potential of *A. lappa* ethanolic extract for the management of PD on the basis of scientific grounds by using a rotenone-induced PD animal model.

MATERIALS AND METHODS

Collection and Authentication of Plant Material

Roots of *Articum lappa* were collected from outskirts of Jaipur, Rajasthan in November 2023. The plant was identified, authenticated and certified (HPSBB/AC/22/088) by Dr. Pankaj Sharma, Senior Scientist, Himachal Pradesh State Biodiversity Board, Shimla, Himachal Pradesh.

Extraction

The process began with the thorough washing of the plant roots to eliminate dirt and other contaminants. After cleaning, the roots were separated and dried in the shade to avoid any potential chemical degradation from sunlight. Once fully dried, the leaves were milled into a coarse powder, which was then passed through sieve No. 14 to ensure uniform particle size. The prepared powdered leaves of *Articum lappa*, weighing 500 grams, were placed into a thimble, a specialized container used for Soxhlet extraction. This thimble was then inserted into the tube of a Soxhlet apparatus, which was set up on a heating mantle to maintain consistent heat for 6 hours. Different solvents—ethyl acetate, methanol, and water—were used in this extraction process, each targeting different compounds based on their solubility. Following the extraction, the resulting extracts were filtered while still hot to prevent any compounds from precipitating as the solution cooled. These filtered extracts were then subjected to evaporation using a rotary vacuum evaporator, which efficiently removed the solvents under reduced pressure without overheating the extracts. The final dried extract samples were stored at low temperatures in a refrigerator to preserve.

Preliminary phytochemical screening

Various extracts of *M. esculenta* leaves were subjected to phytochemical analysis [20]. A series of identification tests were performed to detect presence of alkaloids, flavonoids, saponins, proteins and amino acids, fixed oils and fats, glycosides, tannins and steroids.

Quantitative phytochemical

Total phenolic content (TPC)

A 52 mL volumetric flask containing 9 mL of distilled water was filled with a dilution of 1 mL of extracts of *Articum lappa* roots or standard solutions of gallic acid (20, 40, 60, 80, and 100 g/mL) to assess the total phenolics content (TPC) using the Folin-Ciocalteu test. Using distilled water, a reagent blank was created. The mixture was then mixed before 1 mL of the Folin-Ciocalteu phenol reagent was added. After waiting for five minutes, 0.1 mL of a 7% Na_2CO_3 solution was added to the mixture, bringing the volume up to the required level. A UV/Vis spectrophotometer was used to measure the mixture's absorbance at 550 nm in comparison to the reagent blank after it had been incubated at room temperature for 90

minutes. The total phenolics content was expressed as milligrams of gallic acid equivalents (GAE) [21]

Total flavonoid content (TFC)

The total flavonoid content was determined using the method described in earlier literature. The values were represented as rutin equivalent (RT) per gramme of fraction, with rutin serving as the reference. Rutin was used in rutin concentrations ranging from 1 mg/mL to 1 g/mL to create a standard curve. To perform the analysis, 125 litres of water were mixed with 25 litres of either the sample or the standard, and then 7.5 litres of 5% $NaNO_2$ were added. Five minutes were given for the mixture to react. Then, 250 mL of water were added, followed by the addition of 25 mL of $AlCl_3$ solution and 50 mL of 4% NaOH. To carry out the analysis, 125 litres of water were mixed with 25 litres of either the sample or the standard, and then 7.5 litres of 5% NaNO2 were added. Five minutes were given for the mixture to react. Then, 250 mL of water were added, followed by the addition of 25 mL of $AlCl_3$ solution and 50 mL of 4% NaOH. The resulting mixture was allowed to sit at room temperature for 15 minutes in the dark. Readings of absorbance were recorded at 510 nm. To be sure the analysis was accurate, it was done three times [22].

Antiparkinson activity

Experimental animals

The Albino Wistar rats, which weighed between 180 to 200 gm. Animals were housed in colony cages and kept up under the standard laboratory environment conditions; temperature 25^{o} C, 12 h. Light: 12 h dark cycle and 45-55% relative humidity with free access to food and water ad libitum. Animals were acclimatized to laboratory conditions before the test. Each gathering comprised of six (n = 6) animals. Every one of the trials was done amid the light time frame (8:00 – 16:00 h). Investigation was done as per the rules are given by committee for the purpose of control and Supervision of experiments on Animals (CPCSEA), New Delhi, India. All animal experiments were approved by the Institutional Animal Ethics Committee (IAEC). All animal experiments were approved by the Institutional Animal Ethics Committee (IAEC) of IDMA Lab. Adequate measures were taken to minimize pain and discomfort with animal experimental procedures.

Experimental design (Rotenone-Induced model)

In the study, 36 Albino rats of the middle-aged group were selected and randomly separated into 6 groups, each consisting of 6 animals.

Group-1: The normal control received sunflower oil (1ml/kg; s.c.) along with normal saline (5ml/kg; p.o.) as a vehicle for a period of 28 days.

Group-2: The negative control received rotenone (2 mg/kg; s.c., emulsified in sunflower oil at 2 mg/ml) along with normal saline (5ml/kg; p.o.) as a vehicle for a period of 28 days.

Group-3: The standard control received rotenone (2 mg/kg; s.c., emulsified in sunflower oil at 2 mg/ml) and L-DOPA (10 mg/kg, p.o.) for 28 days.

Group-4: Received rotenone (2 mg/kg; s.c., emulsified in sunflower oil at 2 mg/ml) and a low dose of Ethanolic Extract *A. lappa* (EEAL) (50 mg/kg) orally for 28 days.

Group-5: Received rotenone (2 mg/kg; s.c., emulsified in sunflower oil at 2 mg/ml) and a medium dose of Ethanolic Extract *A. lappa* (EEAL) (100 mg/kg) orally for 28 days.

Group-6: Receive rotenone (2 mg/kg; s.c., emulsified in sunflower oil at 2 mg/ml) and a high dose of Ethanolic Extract *A. lappa* (EEAL) (200 mg/kg) orally for 28 days.

All the groups were given their relevant treatments for 21 days using a gavage needle. Behavioral evaluation was done every week i.e. on day 7, 14, 21, 28. After measuring the behavioral parameters on 28th day animals were humanely killed by cervical dislocation under mild chloroform anesthesia (ketamine (50 mg/kg, i.p). Brains were excised from all the animals for bio- chemical and histopathological analysis to examine the anti-PD effect of the plant extract. For the preparation of tissue homogenate (10% w/v) and biochemical assays brain was isolated and the homogenate was prepared with phosphate buffer.

Statistical Analysis

All the data are expressed in mean ± SEM. The significance of difference in means between control and treated animals was determined by One-way analysis of variance (ANOVA) followed by Bonferroni multiple comparison test.

RESULTS AND DISCUSSION

Qualitative phytochemical

Various phytochemical analysis tests supported that the extracts contain alkaloids, carbohydrates, flavonoids, phenolic compounds, tannins and glycosides, recorded in table 1.

Table 1. Preliminary phytochemical screening

Phyto-constituents	Extracts		
	EE	ME	AsE
Alkaloids	Present	Negative	Positive
Carbohydrates	Absent	Present	Present
Proteins & amino acids	Present	Absent	Absent
Fixed oils & fats	Absent	Absent	Absent
Flavonoids	Present	Present	Present

Phenolic compounds	Present	Present	Present
Tannins	Absent	Present	Present
Glycosides	Present	Present	Present
Saponins	Absent	Absent	Absent
Steroids	Absent	Absent	Absent

AE- Aqueous extract, **EE**- Ethanolic extract, **ME**- Methanolic extract

Quantitative phytochemical

Total phenolic content (TPC)

Phenolic content was measured using the Folin-Ciocalteu reagent in each extract. The results were expressed in gallic acid equivalents (GAE) per gram dry extract weight (Table 2). The results showed that the ethanolic extract exhibited higher TPC as compared to the methanolic and aqueous extracts which are approximately about 73.87 ± 0.20 mg GAE/g for ethanolic extract, 46.83 ± 0.13 mg GAE/g for methanolic extract, and 30.33 ± 0.33[a] mg GAE/g for aqueous extract. Higher phenolic content in the ethanolic extract is responsible for bioactivity; therefore, this extract is expected to exhibit good result in antiparkinson activity.

Total Flavonoid Content (TFC)

Flavonoid contents in root extracts were determined using aluminum chloride in a colorimetric method. The results were expressed in quercetin equivalents (QE) per gram dry extract weight (Table 6.3). The results showed that the ethanolic extract exhibited higher TFC as compared to the methanolic and aqueous extracts which are approximately about 86.90 ± 0.25 mg GAE/g for ethanolic extract, 44.77 ± 0.32 mg GAE/g for methanolic extract, and 22.32 ± 0.20 mg GAE/g for aqueous extract.

Table 2. Total Phenolic Content (TPC) and Total Flavonoid Content (TFC)

Extracts	TPC (mg/g GAE)	TFC (mg/g QE)
EE	73.87 ± 0.20[a]	86.90 ± 0.25[a]
ME	46.83 ± 0.13[b]	44.77 ± 0.32[b]
AE	30.33 ± 0.33[c]	22.32 ± 0.20[c]

AE- Aqueous extract, **EE**- Ethanolic extract, **ME**- Methanolic extract.

Each value represents the mean and standard error mean of three replicates. Different letters denote statistical significance, which was established at $p < 0.05$.

Pharmacological Activity

Neurobehavioral study

Ethanolic extract of *Articum lappa* selected for antiparkinson activity in rats because the results of extractive value, TPC and TFC suggested that ethanolic extract contain higher amount of phenolic and flavonoids that are responsible neuroprotective property.

Behavioral assessment data of rotenone induced anti-Parkinson study revealed that all the groups i.e., EEAL (50, 100 & 200 mg/kg), and levodopa treated showed significant ($P<0.001$) reduction in spontaneous locomotor activity (Table 3) and significant ($P<0.001$) increase in muscle coordination (Table 4) whereas in all groups compared with control (Rotenone treated) group. Animals treated with rotenone (2.5 mg/kg, i.p.) alone for 28 days showed a significant decrease in rearing behavior when compared to vehicle treated group while nonsignificant decrease in grooming behavior on 7th day, significant ($P < 0.001$) decrease in other day in when compared with vehicle treated group. EEAL 50 mg/kg and 100 mg/kg treated group shown nonsignificant increase in grooming behavior on 14th day when compared with rotenone alone treated group. Animals treated with high dose (200 mg/kg) EEAL showed a significant ($P < 0.001$) in rearing and grooming behavior when compared with rotenone alone treated group (Table 5 and 6).

Table 3. Spontaneous Locomotor Activity (in sec.)

S. No.	0 day	7 day	14 day	21 day	28 day
Normal Control	86.67±2.77	88.50±1.565	90.83±1.447	94.17±1.600	98.00±1.592
Rotenone Treated	81.83±2.522$^{###}$	38.33±3.565$^{###}$	24.83±2.688$^{###}$	20.50±2.566$^{###}$	22.67±2.431$^{###}$
EEAL (50 mg/kg)	83.83±2.574***	51.67±2.629***	36.00±2.805***	33.83±2.386**	37.67±2.848**
EEAL (100 mg/kg)	86.67±2.445***	59.00±3.967***	53.33±3.499***	49.50±3.914**	55.17±4.347**
EEAL (200mg/kg)	82.50±6.30***	67.67±3.712***	65.67±3.169**	69.67±3.528**	74.00±3.587**
L-Dopa (10mg/kg)	86.45±3.412***	71.23±2.432***	66.89±2.113***	74.12±3.145***	79.34±2.445***

Table 4. Muscular coordination (in sec.)

S. No.	0 day	7 day	14 day	21 day	28 day
Normal Control	112.00±3.088	112.17±3.30	112.33±4.47	113.33±2.90	113.17±3.439
Rotenone Treated	104.83±2.496$^{###}$	55.00±3.29$^{###}$	41.33±3.54$^{###}$	34.50±2.77$^{###}$	28.83±2.92$^{###}$
EEAL	108.83±2.386***	67.33±4.02***	56.33±3.70**	52.17±2.54**	48.50±3.423**

(50 mg/kg)					
EEAL (100 mg/kg)	101.33±3.432***	74.00±3.32***	62.00±3.80**	57.50±3.62**	61.33±3.106**
EEAL (200mg/kg)	103.17±2.167***	82.17±3.77***	75.33±3.61**	78.67±3.47**	83.67±3.232**
L-Dopa (10mg/kg)	110.00±2.352***	95.33±3.01***	86.00±2.51**	91.17±2.30**	96.17±2.482**

Table 5. Rearing (in Number)

REARING	**0 day**	**7 day**	**14 day**	**21 day**	**28 day**
Normal Control	26.33±1.282	27.17±1.327	26.83±0.872	25.50±0.764	25.33±0.715
Rotenone Treated	23.17±1.249	14.00±1.155###	11.50±1.057###	8.00±0.683###	6.17±0.477###
L-Dopa (10mg/kg)	23.83±0.946	22.17±1.014***	21.00±0.931***	20.33±0.843***	21.33±0.843***
EEAL (50 mg/kg)	22.33±1.256	20.33±0.919***	19.33±1.085***	17.67±1.054***	16.33±0.760***
EEAL (100 mg/kg)	23.33±1.145	21.33±0.955***	20.17±0.872***	19.67±0.667***	19.00±0.775***
EEAL (200mg/kg)	23.67±1.333	22.00±1.238***	20.83±1.195***	20.00±1.095***	20.33±1.022***

Table 6. Grooming (in Number)

GROOMING	**0 day**	**7 day**	**14 day**	**21 day**	**28 day**
Normal Control	9.50±0.847	9.67±0.667	10.00±0.447	9.83±0.703	9.67±0.667
Rotenone Treated	9.33±0.494	7.83±0.477###	6.00±0.365###	4.83±0.307###	3.67±0.211###
L-Dopa (10mg/kg)	9.83±0.601	9.17±0.543***	8.83±0.477***	8.67±0.211***	9.33±0.211***
EEAL (50 mg/kg)	9.17±0.703	8.33±0.615***	7.67±0.615**	6.83±0.307***	6.50±0.224***
EEAL (100 mg/kg)	9.50±0.563	8.50±0.428**	7.83±0.401NS	7.33±0.422***	6.83±0.401***
EEAL (200mg/kg)	10.00±0.730	9.17±0.654***	8.50±0.619***	8.00±0.516***	7.50±0.619***

Biochemical Estimation

The enzymatic and non-enzymatic antioxidant estimations were done. The brain homogenate showed significantly reduced activities of SOD, GSH and CAT while increase in MDA in control group as compared to vehicle treated group. The ethanolic extract of *Articum lappa* showed a significant protection by reducing the elevated levels of MDA (P<0.001) and increasing the SOD (P<0.001), CAT (P<0.001) and GSH (P<0.001) levels as compared to the control group (Table 7).

Table 7. Effect of EEAL on the level of biochemical parameters in rotenone treated rats

Group	MDA	SOD	CAT	GSH
Normal Control	9.50±0.368	350.97±1.134	46.58±2.341	10.76±0.153
Rotenone Treated	57.08±1.359$^{###}$	163.17±2.167$^{###}$	9.89±0.166$^{###}$	0.43±0.031$^{###}$
L-Dopa (10mg/kg)	18.28±0.364	305.58±1.926***	40.36±2.924***	7.48±0.123***
EEAL (50 mg/kg)	48.61±0.852***	182.26±2.163***	14.77±0.681^{ns}	1.84±0.071***
EEAL (100 mg/kg)	33.28±0.268***	219.44±2.029***	28.15±1.014***	4.11±0.046***
EEAL (200mg/kg)	26.47±0.429***	246.14±5.798***	34.40±1.369***	4.91±0.109***

Values are mean ± SEM; n=6 in each group. ###P<0.001 when compared withvehicle control group; ***P<0.001 when compared with rotenone control; One-way ANOVA followed by Bonferroni multiple comparisons test.

CONCLUSION

The study embarked on an insightful exploration reveals that ethanolic extract of roots of *Articum lappa* have anti-Parkinson potential due to presence of high phenolic and flavonoid contents. The investigation commenced by characterizing the physiochemical and phytochemical profile of *Articum lappa*, shedding light on the diverse array of bioactive compounds present within this natural resource. It would be more appropriate to enhance further research on clinical application for improving the plant-based drug industry and the development of new drugs of herbal origin. In view of the above facts, we are concluding that aqueous extract of *Articum lappa* showed to be an antioxidant and showed a promising effect in animals with Parkinson's disease. The further clinical research would be continued its further activity-guided fractionations would flash more lights to the new upcoming research scholars. It paves a way for the emerging biological studies are ot be strengthened in future with pattern for phytomedicines. By pursuing these research directions, the therapeutic potential of *Articum Lappa* extracts can be more fully understood and harnessed, potentially leading to new treatments for Parkinson's disease and other neurodegenerative disorders.

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